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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,642	ATALA ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,12 and 14-33* is/are pending in the application.

4a) Of the above claim(s) *14-22 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12,23-29 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

Applicant's Request for Continued Examination filed 22 March 2006 has been received and entered into the case. Claims 5, 11 and 13 are cancelled. Claims 1-4, 6-10, 12 and 14-33 remain pending, with claims 14-22 and 30-32 being withdrawn from consideration. Claims 1-4, 6-10, 12, 23-29 and 33 have been considered on the merits. All arguments have been fully considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-10, 12, 23-29 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is directed to a method of organ augmentation comprising transiently transfecting a first population of cells with a plasmid encoding angiogenesis modulating agent VEGF; implanting the transiently transfected first population of cells into a target tissue region where the cells will express the VEGF; and co-administering a second population of cells, wherein the second population of cells substantially comprises cells of a different cell type than the first population of cell; thereby inducing assimilation and differentiation of cell in the target region and augmenting organ function.

In claim 1, the relationship between the second step of the method, involving *implanting* the transiently transfected first population of cells into a specific target tissue region, and the third step, involving '*co-administering*' the second population of cells, comes across unclear. Specifically, its not clear if the second population of cells are implanted with the first population to the target tissue region, or

if they are administered with something else, to a different region of the body. Furthermore, because the two cell populations are intended to be implanted together, simultaneously, requiring each population to be implanted/administered in a separate step confuses the intent. It would be remedial to amend the claim so as to state the two cell populations are co-implanted, to the same target tissue region, in single step, for example, "...implanting the first population of transiently transfected cells along with a second population of cells into a target tissue region, wherein the second population of cells..."

Furthermore, in claim 1, the term "substantially comprises" ('...wherein the second population of cells substantially comprises cell of a different cell type...') renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term appears to limit the percentage or proportion of cells within the second population which must be of a different cell type than the first population; however, there is no information in the claim or in the specification to define what percentage or proportion of the second population must be different in order to satisfy the limitation "substantially". Therefore the claim is rendered indefinite because one skilled in the art cannot determine the metes and bounds of the claimed subject matter.

In claim 2, it is unclear if transiently transfecting the cells such that the angiogenesis modulating agent is produced for less than three weeks is an *additional* step ('...wherein the step of transfecting the cells *further* comprises....') or rather, if it is intended to further define the step of transiently transfecting the cells. Additionally, antecedent basis is technically lacking for the limitation "the cells" in the first line of the claim, as there are multiple cell types recited in claim 1. It would be remedial to amend the language to, "...wherein the step of transfecting the first population of cells ~~further~~ comprises transiently transfecting the cells[[,]] such that..."

Claims 6 and 7 are dependent on cancelled claim 5, thus the metes and bounds of these claims cannot be determined. However, it appears claims 6 and 7 should be dependent on amended claim 1, therefore examination has been conducted as such.

Applicant's claim 23 is directed to a method for augmenting organ function, comprising culturing at least a first population of cells on a matrix material to produce an organ construct capable of differentiating *in vivo* to replace or augment organ function; transiently transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent, wherein the second population of cells substantially comprises cells of a different cell type than the first population; and implanting the organ construct and the transfected cells *in vivo* at one target site.

First, the term 'capable of' in the third line of claim 23 ('organ construct capable of differentiating *in vivo*') renders the claim indefinite, as it is unclear if the organ construct actually differentiates *in vivo*, and if so, it is unclear what additional steps or stimulation are required for such, or if it is only required that the organ construct could potentially differentiate *in vivo*. "Capable of" implies a latent property and the conditions for the latent property must be clearly defined. Therefore, it is unclear if the latent property (differentiation *in vivo*) is ever obtained.

Second, the term "substantially comprises" ('...wherein the second population of cells substantially comprises cell of a different cell type...') renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term appears to limit the percentage or proportion of cells within the second population which must be of a different cell type than the first population; however, there is no information in the claim or in the specification to define what percentage or proportion of the second population must be different in order to satisfy the limitation "substantially". Therefore the claim is

rendered indefinite because one skilled in the art cannot determine the metes and bounds of the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-10, 12 and 23-29, 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al, (US 2003/0007954), in view of Lu et al (Circulation, 2001), Atala (US Patent 6,479,064), and Penn et al (US 2004/0161412 A1, as fully supported by provisional applications 60/405274 & 60/424065).

Applicant's claim 1 is directed to a method of organ augmentation comprising transiently transfecting a first population of cells with a plasmid encoding angiogenesis modulating agent VEGF; implanting the transiently transfected first population of cells into a target tissue region where the cells will express the VEGF; and co-administering a second population of cells, wherein the second population of cells substantially comprises cells of a different cell type than the first population of cell; thereby inducing assimilation and differentiation of cell in the target region and augmenting organ function. Claim 2 requires the transiently transfected cells to produce the angiogenesis modulating agent for less than three weeks. Claim 3 requires the first population of cells to comprise undifferentiated cells. Claim 4 requires the first population of cells to comprise vascular endothelial cells. Claim 6 requires the second population of cells to comprise undifferentiated cells. Claim 7 requires the second population of cells to comprise vascular endothelial cells. Claim 8 requires the method to further comprise suspending the

transfected cells in a pharmaceutically acceptable carrier; claim 9 requires the pharmaceutically acceptable carrier to comprise collagen; claim 10 requires the pharmaceutically acceptable carrier to comprise a polymer matrix. Claim 12 requires the first population of cells to comprise myoblasts.

Applicant's claim 23 is directed to a method for augmenting organ function, comprising culturing at least a first population of cells on a matrix material to produce an organ construct capable of differentiating *in vivo* to replace or augment organ function; transiently transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent, wherein the second population of cells substantially comprises cells of a different cell type than the first population; and implanting the organ construct and the transfected cells *in vivo* at one target site. Claim 24 requires the matrix to be decellularized tissue. Claim 25 requires the matrix to be a hydrogel. Claim 26 requires the matrix to be a polymer. Claim 27 requires either the first or second cell populations to comprise myoblasts. Claim 28 requires the angiogenesis modulating agent to be VEGF. Claim 29 requires the method to further comprise assimilating the transfected cells into a tissue layer. Claim 33 requires the organ construct and the transfected cells to be implanted at a plurality of target sites *in vivo*.

Naughton et al teach a method for treatment of ischemic tissue, particularly myocardial ischemia, by producing and implanting a three-dimensional stromal tissue construct to the ischemic region of the heart to promote vascularization of the heart and regeneration of the damaged cardiac muscle cells (which applicant calls organ augmentation) (See Naughton et al, Pg. 2, paragraph 0028). The method of Naughton et al comprises formation of a three-dimensional stromal tissue construct by inoculating stromal cells onto a three-dimensional scaffold; and then implantation of the three-dimensional tissue construct at various locations where the heart tissue was damaged by ischemia so as to allow assimilation of the stromal cells into the natural cardiac tissue (See Naughton et al, Pg. 5, paragraphs 0055-0057). It would further have been obvious to one of ordinary skill in the art, at the time the invention was made, to implant multiple tissue constructs at multiple sites, as needed to correct ischemic damage. One would be

motivated to produce and implant as many tissue constructs as needed to correct all areas of ischemic damage in order to fully treat a patient.

Regarding the material of the three-dimensional scaffold (matrix), Naughton et al teach the three-dimensional scaffold can consist of PGA, collagen, polylactic acid (a polymer) or hyaluronic acid (See Naughton et al, Pg. 2, paragraph 0032). The three-dimensional scaffold is implanted, and thus is considered a pharmaceutically acceptable carrier. One of ordinary skill in the art will further recognize that hydrogels and decellularized tissue are other acceptable scaffold material commonly known and used in the art for *ex vivo* tissue construct formation (See, e.g. Atala, Pg. 1, paragraph 0012), as such use of hydrogels or decellularized tissues would have been obvious to one of ordinary skill in the art at the time the invention was made.

Regarding the types of cells cultured on the three-dimensional scaffold Naughton et al teach the stromal cell populations can comprise fibroblasts as well as tissue specific cells, such as heart cells, particularly cardiac muscle cells and aortic smooth muscle cells (See Naughton et al, Pg. 3, paragraph 0034 & claims 3 and 4). It would have been obvious to one of ordinary skill in the art to more particularly use myoblasts (which are considered undifferentiated cells). Myoblasts are commonly used in the formation of bioartificial muscles (See, e.g. Lu et al, Pg. 595, col. 1) and thus one of ordinary skill in the art would have been motivated to use these precursor cells (undifferentiated cells) as the specific heart cells in the tissue construct of Naughton et al in order to allow for natural differentiation and formation of the cardiac tissues. One would have expected success using myoblasts because their use in bioartificial muscle constructs is well known in the art (See, e.g. Lu et al).

Naughton et al teach additional cells can be added to form the three-dimensional tissue, including endothelial cells (See Naughton et al, Pg. 3, paragraph 0038). It would have been obvious to one of ordinary skill in the art to additionally include endothelial cells, particularly vascular endothelial cells, in the three-dimensional tissue construct of Naughton et al because at the time the invention was made,

inclusion of vascular endothelial cells, in addition to stromal/parenchymal cells, in tissue engineered constructs was known to promote formation of a primitive vascular system (See Atala, col. 2, ln 19-52). Thus, because one of the goals of the tissue construct of Naughton et al is to promote vascularization in the tissue construct, one would be motivated to include the vascular endothelial cells which were known to promote such vasculogenesis (See Naughton et al, Pg. 1, paragraph 0007). Thereby, upon implantation of the tissue construct, Naughton et al effectively co-administers both the stromal cells, which may comprise myoblasts and other tissue specific cells, as well as vascular endothelial cells.

Finally, Naughton et al further teach cells which have been genetically-engineered so as to produce exogenous gene products that promote tissue growth and angiogenesis are desirable for use in the tissue construct; particularly desirable are cells engineered to express vascular endothelial growth factor (VEGF) (See Naughton et al, Pg. 5, paragraphs 0046-0050). While Naughton et al does not provide details on the transfection of the cells with VEGF, at the time the invention was made, means of transfecting cells, including myoblasts, with plasmids encoding VEGF were known in the art. See, for example, Penn et al. Penn et al teach transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, Pg. 7, paragraph 0092). Penn et al also teach that the VEGF can be transiently expressed for any suitable and defined length of time (See Pg. 8, paragraph 0100-0102). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization and minimize systemic effects and hemangioma formation (See Penn et al, Pg. 1, paragraph 0004). With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the

active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence to the contrary, submitting the claimed time period is critical. Thus, based on the teachings of Penn et al, it would have been well within the purview of one of ordinary skill in the art to successfully transfect the myoblasts with a plasmid encoding VEGF prior to culturing the myoblasts on the tissue construct of Naughton et al. Still further, it would have been obvious to one skilled in the art to transfect either the endothelial cells or the myoblasts for seeding onto the tissue construct of Naughton et al. One skilled in the art would have been motivated to transiently transfect either cell population because transient expression by either cell population would result in the presence of VEGF, which is taught to enhance cell growth (See Naughton et al, Pg. 5, paragraph 0050) and to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, Pg. 2, paragraph 0020 & Pg. 3, paragraphs 0044-0045).

Thus, based on the teachings described above, it would have been obvious to one of ordinary skill in the art to create a three-dimensional tissue construct for the augmentation of cardiac tissue damaged by ischemia by culturing a first population of myoblasts and a second population of vascular endothelial cells on a three-dimensional tissue scaffold (matrix), wherein at least one of the cell populations has been transfected with a plasmid encoding for VEGF, and implanting the complete tissue construct at a cardiac tissue site that exhibits ischemic damage, thereby inducing assimilation and differentiation of cells and augmenting organ function. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 25, 26, 29 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meana et al (Burns, 1998), in view of Andree et al (WO 01/89593).

Applicant's claim 23 is directed to a method for augmenting organ function, comprising culturing at least a first population of cells on a matrix material to produce an organ construct capable of differentiating *in vivo* to replace or augment organ function; transiently transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent, wherein the second population of cells substantially comprises cells of a different cell type than the first population; and implanting the organ construct and the transfected cells *in vivo* at one target site. Claim 25 requires the matrix to be a hydrogel. Claim 26 requires the matrix to be a polymer. Claim 29 requires the method to further comprise assimilating the transfected cells into a tissue layer. Claim 33 requires the organ construct and the transfected cells to be implanted at a plurality of target sites *in vivo*.

Meana et al teach a method for producing a cultured skin equivalent, comprising both an epidermal and a dermal component, suitable for use in skin wound closure, particularly full-thickness burn wounds (See Meana et al, abstract). To form the cultured skin equivalent Meana et al culture human fibroblasts (first cell population) with fibrinogen, in the presence of $CaCl_2$, to form a fibroblast-fibrin gel matrix (which applicant calls an organ construct, which is capable of differentiating in vivo to replace or augment organ function); cultured keratinocytes (second cell population) are then seeded onto the fibroblast-fibrin gel to produce the final skin equivalent (See Meana et al, Pg. 622, col. 2); the equivalent can then be implanted *in vivo* at a target tissue site (the damaged skin) and the cells of the equivalent are capable of forming stratified tissue sheets (See Meana et al, Pg. 625, col. 2-629, col. 1). The fibrin gel matrix is considered both a polymer and a hydrogel.

Though Meana et al does not teach transiently transfecting the keratinocytes with a plasmid encoding an angiogenesis modulating agent, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to do so, based on the teachings of Andree et al. Andree et al also focus on preparation of a composition for healing and repairing human and animal tissue, particularly regeneration of skin tissue using keratinocyte culture systems; however Andree et al

teach use of transfected keratinocytes to increase secretion of necessary growth factors to promote survival and regeneration. Specifically, Andree et al teach transfecting keratinocytes with the CMVh EGF-plasmid (encodes the mature EGF polypeptide (See Andree et al, Pg. 20); EGF is an angiogenesis modulating agent (Page 3 of instant application's specification)) and application of the transfected keratinocytes, combined with fibrin, to full-thickness skin wounds. The keratinocytes are *transiently* transfected with the EGF-plasmid, as Andree et al teach decreased expression of EGF over a 14-day period, from 102.14 ug/mL (at 24 hrs) to only 2.24 ug/mL (at day 14) (See Andree et al, paragraph spanning pg. 21-22). Andree et al report use of the transfected keratinocytes resulted in full re-epithelialization of the full thickness wounds, whereas use of non-transfected keratinocytes only showed some re-epithelialization at the edges of the wounds and no re-epithelialization in the center of the wounds (See Andree et al, pg. 23-24, Example 3).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to use the transiently transfected keratinocytes of Andree et al in the skin equivalent taught by Meana et al. One of ordinary skill would have been motivated to use the transiently transfected keratinocytes of Andree et al because Andree et al report superior results with the transfected keratinocytes compared to non-transfected keratinocytes (See Andree et al, Ex. 3), specifically, complete re-epithelialization occurred with the transfected keratinocytes (Group 3) as opposed to only partial and peripheral re-epithelilazation as with the non-transfected keratinocytes (Group 2); therefore, because the goal of Meana et al is to produce a superior skin equivalent, capable of covering large areas of dermal damage, it would have been obvious to use the keratinocytes of Andree et al. One would have expected success using the transfected keratinocytes of Andree et al in the method of Meana et al, because Andree et al teach the transfected keratinocytes do successfully grow in/on a fibrin matrix, and can successfully be implanted/engrafted *in vivo*. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments received 33 March 2006 have been fully considered.

The object to claim 13 is rendered moot due to the cancellation of the claim.

The rejection of claims 1-10 and 12-13 under 35 USC, 112, second paragraph, indefiniteness, has been obviated by the amendment; however, new rejections have been made.

The amendment to claim 1 has obviated the rejection under 35 USC 102(e) over Penn et al.

Regarding the rejection under 35 USC 103(a), applicants argue the amended claims require the first and second cell populations to be of substantially different cell types; thus the rejection of record, which was based on the understanding that within the population of myoblasts treated by Penn et al not all cells would be transfected, thereby resulting in a first population of transfected myoblasts and a second population of non-transfected myoblasts, is withdrawn. Applicants further argue each reference cited individually, stating that none of the references teach implanting two different types of cells (one being transiently transfected to produce VEGF) at a target tissue site. While one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references, the rejection is withdrawn due to the amendment. However, new rejections have been made.

Regarding the double patenting rejection, applicants argue that the copending claims of application 10/292166 are not directed to an obvious variation of the instant claims, specifically the copending claims do not teach or suggest transfecting cells with VEGF, much less teach the importance of transiently transfecting the cells with VEGF. Applicants arguments are found persuasive, and the provisional double patenting rejection is withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER